REMARKS

Reconsideration of this application is respectfully requested.

Claims 1, 5, 6 and 55 are in the application. Through this Amendment, claim 54 has been cancelled, and claim 55 has been amended to change its dependency from claim 54 to claim 1.

In the Official Action, the Examiner rejected claims 54 and 55 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Examiner asserted that the specification does not provide sufficient support for the limitation of the epoxy-activated insoluble support being "not cross-linked" or the support being agarose. In response, claim 54 has been cancelled. In addition, reference is made to para. [0030] of the application as published which lists examples of insoluble supports useable with the subject invention, including "sepharose beads". It is respectfully submitted that claim 55 is in accord with the written description requirement.

Claims 1, 5 and 6 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Grahnen et al. (Eur. J. Biochem., 80, 573-580 (1997)) in view of Spring et al. (U.S. Patent No. 5,643,721) further in view of Degen et al. (U.S. Patent No. 5,567,615). The Examiner admitted that "Grahnen et al. fail to teach the ligand attached to the support via an epoxy linkage." To overcome this deficiency, the Examiner asserted that Spring et al. teach ligands attached to an agarose substrate by an epoxy linker. Further, the Examiner asserted that Degen et al. teach a ligand having a hydroxyl group attached to a polymer support via an epoxy linker. The Examiner concluded:

> Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the apparatus of Grahnen et al., an epoxy linkage between the ligand and the agarose support as taught by Spring et al., in order to provide a simple method of attaching ligands having a hydroxyl group to a substrate by way of a spontaneous covalent attachment as taught by Degen et al. Degen et al. do not specifically teach a bromosulphophthalein ligand being attached to an agarose support. However, Degen et al. teach that epoxy linker attachment is advantageous for ligands having a hydroxyl group and Spring et al. teach that an epoxy linker is advantageous to link ligands to an agarose

> support. Since bromosulphophthalein comprises a hydroxyl group, Degen et al. teach the epoxy linkage would be a simpler and advantageous method of attachment of bromosulphophthalein to a substrate, and Spring et al. teach that it would have been obvious for the substrate that the epoxy linker attaches to, to be an agarose support. Therefore an epoxy linker is advantageously used to attach the ligand to the agarose substrate of Grahnen et al.
>
> The Examiner's assertions are respectfully traversed.

As noted by the Examiner, Grahnen et al. do not use an epoxy linker to attach bromosulphophthalein (BSP) to an insoluble support. Rather, Grahnen et al. relies on sodium borohydride, presumably acting as a reducing agent, to cause the BSP to link to the support. (P. 754, bottom of left column). It is noted that Grahnen et al. uses BSP for extracting porcine ligandin from porcine liver cytosol. (See, Abstract at p. 573 of Grahnen et al.).

The Examiner asserted that it would have been obvious to modify Grahnen et al. to use an epoxy linker to attach the BSP to an insoluble support. However, at pp. 579-580, Grahnen et al. discuss the results of their testing and found that porcine ligandin "display a 30-50-fold higher specific activity" than rat or human ligandin. Grahnen et al. noted that "[t]his diversity can in part be due to species differences but it should be emphasized that the observed difference could also be due to differences in the isolation methods as mentioned above. The present isolation method does not, however, discriminate between different isomeric forms with closely related isoelectric points." Grahnen et al. further indicate that it has been "recently reported that there is a poor correlation between a bromosulphophthalein-binding technique and immunological methods for the quantification" of certain protein. It is thus clear that the binding characteristics of BSP are alterable. Due to this unpredictability, one skilled in the art following Grahnen et al. would not look to alter the Grahnen et al. procedure and utilize epoxy linkers.

Under *KSR*, a rationale must be provided for supporting an obviousness rejection. MPEP §2143 sets forth seven possible rationales for supporting an obviousness rejection. Upon review of the Office Action, it appears that the Examiner is relying on the fourth listed rationale

explained in MPEP §2143(D): the rationale directed to applying a known technique to a known device ready for improvement to yield predictable results. MPEP §2143(D) sets forth requirements for satisfying the rationale. Included in the requirements is MPEP §2143(D)(III) which requires that the Examiner may make "a finding that one of ordinary skill in the art would have recognized that applying the known technique would have yielded predictable results". Thus, there must be some showing of predictability in the obviousness rejection to satisfy *KSR*.

As indicated in Grahnen et al., the binding characteristics of BSP are unpredictable. Grahnen et al. disclose a specific technique for linking BSP to an insoluble support. There is no predictability in the characteristics of the resulting BSP in changing that linking methology, specifically by using an epoxy linker. As set forth at MPEP §2143.01(III), "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." It is respectfully submitted that Grahnen et al. can not be modified to use an epoxy linker as suggested by the Examiner. Accordingly, it is respectfully submitted that claim 1, along with dependent claims 5 and 6, are patentable over Grahnen et al., Spring et al. and Degen et al., each taken alone or in combination.

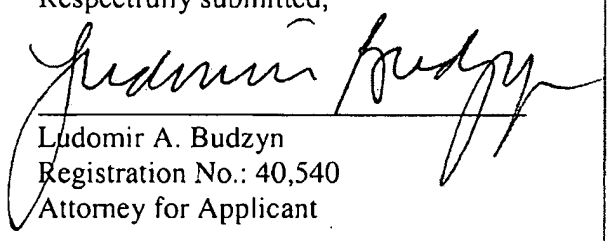
Claims 54 and 55 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Grahnen et al. in view of Spring et al. further in view of Degen et al. and further in view of Travis et al. (U.S. Patent No. 4,093,612).

Travis et al. describes a procedure for removing albumin from fluid through the use of a Color Index Reactive Dye ("CRD"). (Col. 2, ll. 28-30). The structure of the CRD is critical to Travis et al. to achieve the proper removal of albumin from fluid. In fact, Travis et al. states that the coupling procedures of the support with the CRD "depend upon the reaction of a halo group on the triazine moiety with a labile group on the support phase." (Col. 5, ll. 19-22). Alternatively, where a CRD possesses a "labile amino group", coupling may be carried out by activating the support phase with alkaline cyanogen bromide and reacting the activated support

with the dye. (Col. 5, ll. 23-33). Thus, to provide the proper binding, Travis et al. require that the binding material (i.e., the CRD) either have (1) a halo group on a triazine moiety, or (2) a primary amino group, where the support is first activated with the cyanogen bromide. Accordingly, Travis et al. does not overcome the deficiencies noted above of Grahnen et al., notably with respect to the use of an epoxy linker. It is respectfully submitted that claim 55 is patentable over Grahnen et al., Spring et al., Degen et al. and Travis et al., each taken alone or in combination.

Favorable action is earnestly solicited. If there are any questions or if additional information is required, the Examiner is respectfully requested to contact Applicant's attorney at the number listed below.

Respectfully submitted,



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